

U.S.S.N. 09/887,496
BANERJEE *et al.*
AMENDMENT

REMARKS

A check in the amount of \$180.00 for the fee for a Supplemental Information Disclosure Statement is enclosed. Any fees that may be due in connection with this application may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

The specification is amended to correct obvious typographical, spelling and formatting errors and to produce grammatical clarity. In particular the amendments to the paragraph page 3, line 3-10, adds the inadvertently omitted known formula of RPR 106541 (see, *e.g.*, Warne (2000) *Emerging Drugs* 5(2):231-239, copy enclosed with Supplemental Information Disclosure Statement). No new matter has been added. Included as an attachment is a marked-up version of the specification paragraphs, per 37 C.F.R. §1.121.

Claims 1-83, 87-89, 93 and 99-121 are presently pending in this application. Claims 65-68, 93, 113-116, 120 and 121 are withdrawn from consideration as allegedly being directed to a non-elected species. Claims 1, 63, 95 and 117 are amended herein. Basis for the amendments to claims 1 and 117 may be found, for example, in the specification at page 3, lines 30-31. No new matter has been added.

A Change of Address Notification accompanies this Amendment.

A Supplemental Information Disclosure Statement also accompanies this Amendment.

TRAVERSAL OF RESTRICTION REQUIREMENT

The Office Action states that the previous Restriction Requirement is proper and made final. Applicant submitted a Petition under 37 C.F.R. §1.144 on June 17, 2002, *i.e.*, within two months of the mailing date of the instant Action, for reconsideration of the Restriction Requirement as between Groups I and III, and as between Groups II and IV.

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Applicant respectfully requests reconsideration of the Restriction Requirement in view of the following remarks. The Office Action, mailed April 24, 2002, urged that the Restriction Requirement is based on the allegation that the various Groups are patentably distinct because they have different modes of operation. It is respectfully submitted that the Restriction Requirement as between groups I and III, and as between groups II and IV, is improper.

Restriction of Groups I and III

It is respectfully submitted that the Restriction Requirement as between Group I and Group III is improper because the Groups are related as a combination/subcombination.

As stated in MPEP 806.05(c), paragraphs 1 and 3;

In order to establish that combination and subcombination inventions are distinct, two-way distinctness must be demonstrated.

....

The inventions are distinct if it can be shown that a combination as claimed:

(A) does not require the particulars of the subcombination as claimed for patentability (to show novelty and unobviousness), and

(B) the subcombination can be shown to have utility either by itself or in other and different relations.

When these factors cannot be shown, such inventions are not distinct.
(Emphasis added.)

It is noted that the two parts of the test for distinctness of a combination and subcombination are to be applied in conjunction. Both (A) and (B) must be satisfied for restriction to be proper. If either one or both of conditions (A) or (B) are not met, then the inventions are not distinct and restriction is not proper.

Group I is directed to pharmaceutical compositions containing formoterol, or a derivative thereof, and a steroidal anti-inflammatory agent, or a derivative thereof. Group III is directed to pharmaceutical compositions containing formoterol, or a derivative thereof; a steroidal anti-inflammatory agent, or a derivative thereof; and one or more of (a) to (j) as follows: (a) a β_2 -

adrenoreceptor agonist; (b) a dopamine (D₂) receptor agonist; (c) an IL-5 inhibitor; (d) an antisense modulator of IL-5; (e) a tryptase inhibitor; (f) a tachykinin receptor antagonist; (g) milrinone or milrinone lactate; (h) a leukotriene receptor antagonist; (i) a 5-lipoxygenase inhibitor; or (j) an anti-IgE antibody. Hence, Group III is a combination and Group I is a subcombination thereof.

Since the two Groups are related as a combination/subcombination, a showing of two-way distinctness is required. In the instant case, if the compositions of Group I are deemed free of the prior art, the compositions of Group III will necessarily be free of the prior art. Thus, a showing of 2-way distinctness cannot be made. Therefore, the compositions of Group III and the compositions of Group I are not restrictable.

Also, if the claims are restricted into these two Groups, applicant ultimately could be granted two patents, one that includes claims encompassing pharmaceutical compositions containing formoterol, or a derivative thereof, and a steroidal anti-inflammatory agent, or a derivative thereof; and another with claims directed to pharmaceutical compositions containing formoterol, or a derivative thereof, a steroidal anti-inflammatory agent, or a derivative thereof, and at least one more active agent as recited above, that expire on different dates. If the claims to the combinations (Group III) issued first, a later issuing patent encompassing the subcombination (Group I) could not be held to constitute obvious-type double patenting over the earlier issuing patent. See MPEP 806, which states:

[w]here restriction is required by the Office double patenting cannot be held, and thus, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

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See, also MPEP 804.01, which states:

35 U.S.C. 121 authorizes the Commissioner to restrict the claims in a patent application to a single invention when independent and distinct inventions are presented for examination. The third sentence of 35 U.S.C. 121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent. The 35 U.S.C. 121 prohibition applies only where the Office has made a requirement for restriction. The prohibition does not apply where the divisional application was voluntarily filed by the applicant and not in response to an Office requirement for restriction. This apparent nullification of double patenting as a ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restrictions where the claims define essentially the same invention in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

It is alleged that Groups I and III are directed to unrelated subject matter since the subject matter of the Groups allegedly have different modes of operation. Applicant respectfully disagrees. The compositions of Groups I and III are intended for the same use (*i.e.*, administration to a patient in need thereof for treatment, prevention, or amelioration of one or more symptoms of a bronchoconstrictive disorder). Therefore, the compositions of both Groups I and III have the same mode of operation. Furthermore, as described in detail above, the compositions of Groups I and III are related as a combination/subcombination for which a showing of two-way distinctness is required. The Office Action fails to provide such a showing.

Since such restriction is improper, reconsideration and withdrawal of the restriction requirement as between Group I and Group III is, therefore, respectfully requested.

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Groups II and IV

Applicant traverses the restriction requirement as between Group II, which is directed to methods of treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders by administration of pharmaceutical compositions containing formoterol, or a derivative thereof, and a steroidal anti-inflammatory agent, or a derivative thereof; and Group IV, which is directed to methods of treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders by administration of pharmaceutical compositions containing formoterol, or a derivative thereof; a steroidal anti-inflammatory agent, or a derivative thereof; and administration of one or more of (a) to (j) as follows: (a) a β_2 -adrenoreceptor agonist; (b) a dopamine (D_2) receptor agonist; (c) an IL-5 inhibitor; (d) an antisense modulator of IL-5; (e) a tryptase inhibitor; (f) a tachykinin receptor antagonist; (g) milrinone or milrinone lactate; (h) a leukotriene receptor antagonist; (i) a 5-lipoxygenase inhibitor; or (j) an anti-IgE antibody; simultaneously with, prior to or subsequent to the formoterol/steroidal anti-inflammatory agent composition. Group IV (the combination) thus is directed to methods using the compositions used in the methods of Group II (the subcombination) plus administration of at least one more active agent.

Therefore, Group IV is related to Group II as a combination/subcombination for which a showing of two-way distinctness is required (see, MPEP 806.05(c), paragraphs 1 and 3, *supra*). In the instant case, if the methods of Group II are deemed free of the prior art, the methods of Group IV will necessarily be free of the prior art. Thus, a showing of 2-way distinctness cannot be made. Therefore, the methods of Group IV and methods of Group II are not restrictable.

Also, if the claims are restricted into these two Groups, applicant ultimately could be granted two patents, one that includes claims encompassing methods of treatment, prevention, or amelioration of one or more symptoms of

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bronchoconstrictive disorders by administration of pharmaceutical compositions containing formoterol, or a derivative thereof, and a steroidal anti-inflammatory agent, or a derivative thereof; and another with claims directed to methods of treatment, prevention, or amelioration of one or more symptoms of bronchoconstrictive disorders by administration of pharmaceutical compositions containing formoterol, or a derivative thereof, and a steroidal anti-inflammatory agent, or a derivative thereof, and administration of at least one more active agent, as described above, that expire on different dates. If the claims to the combinations (Group IV) issued first, a later issuing patent encompassing the subcombination (Group II) could not be held to constitute obvious-type double patenting over the earlier issuing patent. See MPEP 806, paragraph 3, and MPEP 804.01 (*supra*).

It is alleged that Groups II and IV are directed to unrelated subject matter since the subject matter of the Groups allegedly have different modes of operation. Applicant respectfully disagrees. The methods of Groups II and IV are directed to administration of bronchodilating compositions containing formoterol, or a derivative thereof, and a steroidal anti-inflammatory agent, or a derivative thereof; and administration of bronchodilating compositions containing formoterol, or a derivative thereof, and a steroidal anti-inflammatory agent, or a derivative thereof, and administration of at least one more active agent, as described above, respectively, for treatment, prevention, or amelioration of one or more symptoms of a bronchoconstrictive disorder. Therefore, the methods of both Groups II and IV have the same mode of operation. Furthermore, as described in detail above, the methods of Groups II and IV are related as a combination/subcombination for which a showing of two-way distinctness is required. The Office Action fails to provide such a showing.

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Since such restriction is improper, reconsideration and withdrawal of the restriction requirement as between Group II and Group IV is, therefore, respectfully requested.

As noted above, applicant has submitted a Petition pursuant to 37 C.F.R. §1.144 that was timely filed within 2 months from the mailing of the Office Action requesting reconsideration of the Restriction Requirement as between Groups I and III, and as between Groups II and IV.

OBJECTION TO CLAIM 63

The Office Action objects to claim 63 for recitation of "(BMP)" and "(BDP)." Claim 63, as amended herein, does not recite "(BMP)" or "(BDP)," thereby overcoming this objection. The scope of claim 63 has not been altered by this amendment, and no subject matter has been surrendered thereby.

REJECTION OF CLAIMS 63-72 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 63-72 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for recitation of "RPR 106541" in claim 63. As amended herein, claim 63 provides the known formula of this compound (see, *e.g.*, Warne (2000) *Emerging Drugs* 5(2):231-239, copy enclosed with Supplemental Information Disclosure Statement). No new matter has been added, nor has the scope of these claims been altered by this amendment to claim 63. No subject matter has been surrendered thereby. w/d

REJECTION OF CLAIMS 1-64, 69-83, 87-89, 99-112 AND 117-119 UNDER 35 U.S.C. §103(a)

Claims 1-64, 69-83, 87-89, 99-112 and 117-119 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.* (U.S. Patent No. 6,150,418) in view of Bartow *et al.* ((1998) *Drugs* 55(2):303-322) and the PDR (Physician's Desk Reference) entry for Flovent®. The Office Action alleges that Hochrainer *et al.* teaches formoterol compositions suitable for storage; Bartow *et al.* teaches use of formoterol in conjunction with a corticosteroid; and that the PDR entry for Flovent® teaches fluticasone propionate as a corticosteroid for treatment of asthma. The Office Action

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further alleges that combination of the teachings of these references results in the instantly-claimed compositions. Applicant respectfully traverses this rejection.

Relevant Law

[I]n order to establish a *prima facie* case of obviousness, there must be evidence, preferably a teaching, suggestion, incentive or inference from the cited art or in the form of generally available knowledge that one of ordinary skill would have been led to modify the relevant teaching to arrive at what is claimed. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

In addition, unexpected properties must always be considered in the determination of obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The instant claims

Instant claim 1 is directed to a pharmaceutical composition, containing (i) formoterol, or a derivative thereof; and (ii) a steroidal anti-inflammatory agent, or a derivative thereof;

in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

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Instant claims 2-77, 99-108 are directed to pharmaceutical compositions and are dependent on claim 1.

Claim 78 is directed to a kit, containing:

- (a) an aqueous composition comprising (i) formoterol or a derivative thereof, and (ii) a steroidal anti-inflammatory agent or a derivative thereof, formulated for single dosage administration; and
- (b) a nebulizer.

Claims 79 and 80, 109, 110 are directed to kits and are dependent on claim 78.

Claim 81 is directed to a combination containing;

- (a) the pharmaceutical composition of claim 1 formulated for single dosage administration; and
- (b) a vial.

Claims 82 and 83, 111, 112 are directed to combinations and are dependent on claim 81.

Claim 87-89 are directed to articles of manufacture containing the compositions of claims 1, 73 and 74, respectively.

Claim 117 is directed to a combination, containing:

a composition comprising formoterol, or a derivative thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, and the composition is formulated at a concentration for direct administration to a subject in need thereof; and
a composition comprising a bronchodilating steroid, or a derivative thereof.

Claims 118-119 are directed to combinations and are dependent on claim 117.

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The teachings of Hochrainer *et al.* and differences from the instant claims

Hochrainer *et al.* (U.S. Patent No. 6,150,418) teaches a "liquid active substance concentrate" containing formoterol in the form of its free base or in the form of one of the pharmacologically acceptable salts or addition products (adducts) thereof as active substance. This "liquid active substance concentrate" is taught as a "highly concentrated" (*i.e.*, greater than 10 mg/mL, preferably 75 to 500 mg/mL) solution or suspension that is stable for a period of several months possibly up to several years without any deterioration in the pharmaceutical quality (see, *e.g.*, column 1, lines 55-61; column 2, lines 4-7; and claim 1).

This patent teaches that it is the high concentration that allows for the stability of the concentrate. Hochrainer *et al.* does not teach or suggest stable, aqueous compositions containing formoterol formulated at a concentration for direct administration to a subject in need thereof, or formulated for single dosage administration.

The "highly concentrated" "liquid active substance concentrate" of Hochrainer *et al.* is not suitable for direct administration to a subject, nor formulated for single dosage administration. See, *e.g.*, column 2, lines 1-4:

The term "highly concentrated" means a concentration of the active substance which is usually too high to enable the corresponding solution or suspension to be used therapeutically for inhalation without being diluted.

See also, *e.g.*, column 1, lines 47-52:

The active substance concentrate according to the invention may be converted, by diluting with a pharmacologically acceptable liquid which optionally contains pharmaceutical adjuvants and additives, into a pharmaceutical preparation (aerosol formulation) which is converted by means of a nebuliser into an inhalable aerosol.

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Therefore, the "liquid active substance concentrate" of Hochrainer *et al.* is merely a means for storage of formoterol, and is not formulated at a concentration for direct administration to a subject in need thereof, nor formulated for single dosage administration.

In contrast, the pharmaceutical compositions of the instant claims are formulated in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid contains water, and the composition is formulated at a concentration suitable for direct administration to a subject in need thereof, nor formulated for single dosage administration. Hochrainer *et al.* does not teach or suggest these compositions.

The cited reference teaches a "liquid active substance concentrate" that must be diluted prior to administration to a subject in need thereof. Hochrainer *et al.* neither teaches or suggests that the "pharmaceutical preparation" resulting from dilution of the "liquid active substance concentrate" is stable during long term storage. To the contrary, the cited reference teaches that:

In the past it has been found that liquid aerosol formulations of formoterol are not suitable for use in inhalers intended for ambulatory inhalation treatment since *formoterol cannot be stored in a sufficiently stable manner in solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time.* (emphasis added)

See, column 1, lines 30-35 of the cited reference. Thus, Hochrainer *et al.* teaches away from the claimed subject matter. Instant claim 1 is directed to a pharmaceutical composition containing (i) formoterol, or a derivative thereof; and (ii) a steroidal anti-inflammatory agent, or a derivative thereof; in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, and the composition is formulated at a concentration for direct administration to a subject in need thereof. The cited reference teaches that liquid aerosol formulations of formoterol formulated at a concentration for direct administration to a subject in need thereof are not stable during long term storage.

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A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed subject matter. See, *e.g.*, *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). A *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. See, *e.g.*, *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

Therefore, Hochrainer *et al.* does not teach or suggest the pharmaceutical compositions of the instant claims, and the instant claims cannot be *prima facie* obvious over the teachings of this reference.

The teachings of Bartow *et al.* and the PDR entry for Flovent® do not cure the defects in the teachings of Hochrainer *et al.*

Bartow *et al.* and the PDR entry for Flovent® do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for Flovent® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. Neither Bartow *et al.* nor the PDR teach or suggest modification of the "liquid active substance concentrate" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions of the instant claims. Instant claim 1 recites that the composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, the instant claims are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.* and the PDR.

The Office Action fails to set forth a *prima facie* case of obviousness

In order to establish a *prima facie* case of obviousness, the cited references must provide a teaching or suggestion that would motivate one of

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ordinary skill in the art to do what applicant has done. Applicant respectfully submits that no such teaching or suggestion exists in the cited references. Hochrainer *et al.* teaches a "liquid active substance concentrate" that must be diluted prior to administration to a subject in need thereof, and teaches away from the instantly claimed pharmaceutical compositions. Bartow *et al.* and the PDR do not cure the defects of Hochrainer *et al.* Therefore, the instant claims are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.* and the PDR.


Applicant respectfully requests reconsideration and removal of this rejection.

* * *

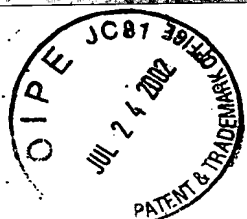
In view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Banerjee *et al.*
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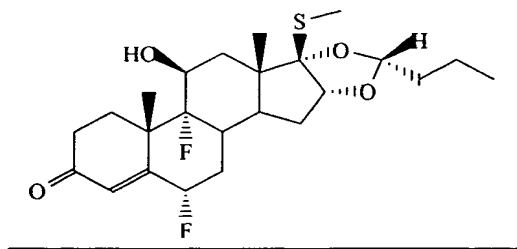
MARKED UP PARAGRAPHS AND CLAIMS IN ACCORDANCE WITH
37 C.F.R. §1.121

IN THE SPECIFICATION:

Please amend the specification as follows:

Please amend the paragraph on page 3, lines 3-10, as follows:

Other prophylactic therapeutics for use in treatment of bronchoconstrictive disorders include steroidal anti-inflammatory agents such as beclomethasone dipropionate (BDP), beclomethasone monopropionate (BMP), flunisolide, triamcenolone acetonide, dexamethasone, tipredane, ciclesonid, mometasone, mometasone furoate (Asmanex® Twisthaler™, Shering-Plough Corporation, Kenilworth, NJ), RPR 106541 having the formula



fluticasone, fluticasone propionate and budesonide. These agents can be formulated for inhalation therapy.

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MARKED UP PARAGRAPHS AND CLAIMS

Please amend the paragraph on page 9, lines 21-29, as follows:

As used herein, a nebulizer is an instrument that is capable of generating very fine liquid [droplet] droplets for inhalation into the lung. Within this instrument, the nebulizing liquid or solution is atomized into a mist of droplets with a broad size distribution by methods known to those of skill in the art, including, but not limited to, compressed air, ultrasonic waves, or a vibrating orifice. Nebulizers may further contain, *e.g.*, a baffle which, along with the housing of the instrument, selectively removes large droplets from the mist by impaction. Thus, the mist inhaled into the lung contains fine aerosol droplets.

Please amend the paragraph beginning on page 10, line 19, through the paragraph on page 11, line 24, as follows:

As used herein, pharmaceutically acceptable derivatives of a compound include salts, esters, enol ethers, enol esters, acids, bases, solvates, hydrates or prodrugs thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethyl-benzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates,

MARKED UP PARAGRAPHS AND CLAIMS

tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula $C=C(OR)$ where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl [ar] and heterocyclyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula $C=C(OC(O)R)$ where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl [ar] and heterocyclyl. Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecule, preferably 1 to about 100, more preferably 1 to about 10, most preferably one to about 2, 3 or 4, solvent or water molecules. Formoterol salts and hydrates are used in certain embodiments herein.

Please amend the paragraph on page 16, lines 11-19, as follows:

In one embodiment, the β_2 -adrenoreceptor agonist [in] is formoterol, or a pharmaceutically acceptable derivative thereof. In other embodiments, the formoterol for use in the compositions provided herein is formoterol fumarate. Formoterol refers to 2-hydroxy-5-((1RS)-1-hydroxy-2-(((1RS)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide; or a stereoisomer thereof. The term formoterol also refers herein to the single enantiomers 2-hydroxy-5-((1S)-1-hydroxy-2-(((1S)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide and 2-hydroxy-5-((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)-amino)ethyl)formanilide.

Please amend the paragraph on page 17, lines 9-17, as follows:

The compositions provided herein further contain, in addition to a β_2 -adrenoreceptor agonist, including formoterol, a [seroidal] steroidal anti-

MARKED UP PARAGRAPHS AND CLAIMS

inflammatory agent, including, but not limited to, budesonide or fluticasone propionate. Budesonide is (RS)-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butraldehyde. Budesonide also refers to the (R) isomer, the (S) isomer, and mixtures thereof. Fluticasone propionate refers to (6 α ,11 β ,16 α ,17 α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxo-propoxy)androsta-1,4-diene-17-carbothioic acid, S-fluoromethyl ester.

Please amend the paragraph beginning on page 19, line 5, through the paragraph on page 20, line 17, as follows:

In other of the above embodiments, the compositions further contain a buffer, including, but not limited to, citric acid/phosphate, acetate, barbitol, borate, Britton-Robinson, cacodylate, citrate, collidine, formate, maleate, McIlvaine, phosphate, Prideaux-Ward, succinate, citrate-phosphate-borate (Teorell-Stanhagen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-aminoethanesulfonic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BIS-TRIS PROPANE (1,3-bis(tris(hydroxymethyl)methylamino)propane), BES (N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS (4-(N-morpholino)butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamino)-2-hydroxypropanesulfonic acid), TRIZMA® (tris(hydroxymethylaminomethane), HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonic acid), POPSO (piperazine-N,N'-bis(2-hydroxypropanesulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N'-(3-propanesulfonic acid), TRICINE (N-tris(hydroxymethyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-

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hydroxyethyl)glycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanesulfonic acid)), TAPS (N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid), AMPD (2-amino-2-methyl-1,3-propanediol), and/or any other buffers known to those of skill in the art. In one embodiment, the buffer is citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer. In another embodiment, the buffer is a citrate buffer (citric acid/sodium citrate). The buffer concentration has been found herein to affect the stability of the composition. Buffer concentrations for use herein include from about 0 or 0.01 mM to about 150 mM, or about 1 mM to about 20 mM. In one embodiment, the buffer concentration is about 5 mM. In another embodiment, the buffer concentration is about 1 mM to about 50 mM, or about 20 mM. The kinetic-pH profile of formoterol is dependent on buffer concentration. At low and approximately neutral conditions, increasing the buffer concentration from 5 mM to 20 mM increased the [rated] rate constant [of decomposition] of decomposition significantly. However, no noticeable differences in rate constant were observed in the pH region of about 4.5 to about 5.5 with increasing buffer concentration from 5 mM to 20 mM. The particular buffer and buffer concentration of a given composition for long term storage provided herein may be determined empirically using standard stability assays well known to those of skill in the art (see, *e.g.*, the Examples).

Please amend the paragraph beginning on page 20, line 29, through the paragraph on page 21, line 28, as follows:

In embodiments where the pharmacologically suitable fluid is a saline solution, tonicity adjusting agents may be added to provide the desired ionic strength. Tonicity adjusting agents for use herein include those which display no or only negligible pharmacological activity after administration. Both inorganic and organic tonicity adjusting agents may be used in the compositions provided herein. Tonicity adjusting agents include, but are not limited to, ammonium carbonate, ammonium chloride, ammonium lactate, ammonium

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nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bismuth sodium tartrate, boric acid, calcium chloride, calcium disodium edetate, calcium gluconate, calcium lactate, citric acid, dextrose, diethanolamine, dimethylsulfoxide, edetate disodium, edetate trisodium monohydrate, fluorescein sodium, fructose, galactose, glycerin, lactic acid, lactose, magnesium chloride, magnesium sulfate, mannitol, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide, potassium nitrate, potassium phosphate, potassium sulfate, [propylene] propylene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfite, sodium borate, sodium bromide, sodium cacodylate, sodium carbonate, sodium chloride, sodium citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate, sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium sulfite, sodium tartrate, sodium thiosulfate, sorbitol, sucrose, tartaric acid, triethanolamine, urea, urethan, uridine and zinc sulfate. In certain embodiments, the tonicity adjusting agent is sodium chloride, which is present at a concentration of from about 0 mg/mL to about 10, 15 or 20 mg/mL. In further embodiments, the compositions contain sodium chloride at a concentration of from about 0 mg/mL to about 7.5 mg/mL. In another embodiment, the compositions contain sodium chloride at a concentration of 0 mg/mL, 1.5 mg/mL, 6.8 mg/mL or 7.5 mg/mL. In these embodiments, the pharmacologically suitable fluid is aqueous saline.

Please amend the paragraph beginning on page 25, lines 11-21, as follows:

In certain embodiments herein, the emulsifier(s) is (are) a polyoxyethylene sorbitan fatty ester or polysorbate, including, but not limited to, polyethylene sorbitan monooleate (Polysorbate 80), polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate), polysorbate 65 (polyoxyethylene (20) sorbitan tristearate), polyoxyethylene (20) sorbitan mono-oleate,

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polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate; sorbitan monostearate; sorbitan tristearate; sorbitan monolaurate; sorbitan mono-oleate; or sorbitan monopalmitate. In further embodiments, the emulsifier(s) is (are) polysorbate 80, sorbitan monolaurate or polyoxyethylene (20) sorbitan [nmonolaurate] monolaurate.

Please amend the paragraph on page 27, lines 14-23, as follows:

The compositions provided herein are prepared by procedures well known to those of skill in the art. For example, a solution formulations may be prepared by the procedure of EXAMPLE 1. Briefly, polyethylene glycol 400 and/or [propylene] propylene glycol, and a preservative, such as vitamin E TPGS, are mixed at about 42 °C until a homogeneous solution forms. The temperature is lowered and the steroidal anti-inflammatory agent is added. In a second vessel, formoterol fumarate dihydrate and the remaining ingredients are dissolved in approximately 70% water. The two solutions are mixed and the resulting solution is diluted with water to the desired volume.

Please amend the paragraph on page 28, lines 2-4, as follows:

Standard physiological, pharmacological and biochemical procedures are available for testing the compositions provided herein to identify those that possess [bronchodilatory] bronchodilatory activity.

Please amend the paragraph on page 34, lines 13-23, as follows:

Polyethylene glycol 400 and/or propylene glycol and vitamin E TPGS were mixed in a stainless steel container with heating at about 42 °C until a homogeneous [liquid] liquid formed. While maintaining the liquid phase, the temperature was lowered and the steroid active ingredient, *e.g.*, budesonide or fluticasone propionate, was added. The [mixing] mixing was [continued until] continued until all of the drug substance had dissolved. In another container all other ingredients, including formoterol fumarate dihydrate, were mixed with about 70% water until a clear solution formed. The two solutions were mixed

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together until a homogeneous clear solution formed. The volume was made up with water and the solution was mixed to give the desired composition.

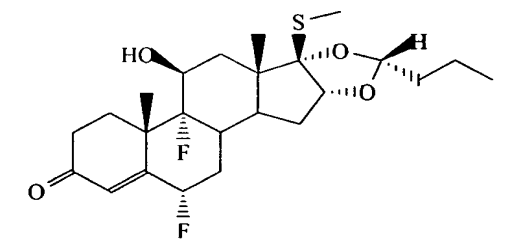
IN THE CLAIMS:

Please amend claims 1, 63, 95 and 117 as follows:

1. (Amended) A pharmaceutical composition, comprising (i) formoterol, or a derivative thereof; and (ii) a steroidal anti-inflammatory agent, or a derivative thereof;

in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, [and] the fluid comprises water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

63. (Amended) The pharmaceutical composition of claim 1, wherein the steroidal anti-inflammatory agent is beclomethasone dipropionate [(BDP)], beclomethasone monopropionate [(BMP)], flunisolide, triamcinolone acetonide, dexamethasone, tipredane, ciclesonid, rofleponide, mometasone, mometasone furoate, RPR 106541 having the formula



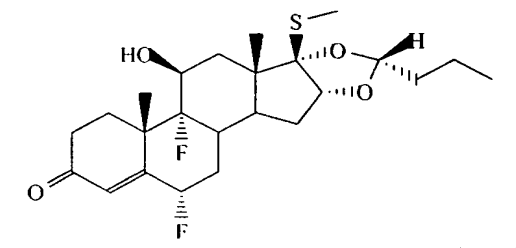
fluticasone or fluticasone propionate, or budesonide, or a derivative thereof.

95. (Amended) The method of claim 94, wherein the steroidal anti-inflammatory agent is beclomethasone dipropionate [(BDP)], beclomethasone monopropionate [(BMP)], flunisolide, triamcinolone acetonide, dexamethasone, tipredane, ciclesonid, rofleponide, mometasone, mometasone furoate, RPR 106541 having the formula

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fluticasone or fluticasone propionate, or budesonide, or a derivative thereof.

117. (Amended) A combination, comprising:

a composition comprising formoterol, or a derivative thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, [and] the fluid comprises water, and the composition is formulated at a concentration for direct administration to a subject in need thereof; and

a composition comprising a bronchodilating steroid, or a derivative thereof.